Pleiotrophin

Pleiotrophin (PTN) also known as heparin-binding brain mitogen (HBBM) or heparin-binding growth factor 8 (HBGF-8) or neurite growth-promoting factor 1 (NEGF1) or heparin affinity regulatory peptide (HARP) or heparin binding growth associated molecule (HB-GAM) is a protein that in humans is encoded by the PTN gene.

Pleiotrophin is an 18-kDa growth factor that has a high affinity for heparin. It is structurally related to midkine and retinoic acid induced heparin-binding protein.

Function

Pleiotrophin was initially recognized as a neurite outgrowth-promoting factor present in rat brain around birth and as a mitogen toward fibroblasts isolated from bovine uterus tissue.

Together with midkine these growth-factors constitute a family of (developmentally regulated) secreted heparin-binding proteins now known as the neurite growth-promoting factor (NEGF) family. During embryonic and early postnatal development, pleiotrophin is expressed in the central and peripheral nervous system and also in several non-neural tissues, notably lung, kidney, gut and bone.

Pleiotrophin is also expressed by several tumor cells and is thought to be involved in tumor angiogenesis.

In the adult central nervous system, pleiotrophin is expressed in an activity-dependent manner in the hippocampus where it can suppress long term potentiation induction.

Pleiotrophin expression is low in other areas of the adult brain, but it can be induced by ischemic insults or targeted neuronal damaged in the entorhinal cortex or in the substantia nigra pars compacta.

Knudsenet al. developed a preclinical orthotopic xenograft tumor resection model in rats with integrated 18F-FET PET/CT imaging. Primary and recurrent tumors were subject to bulk and single cell RNA sequencing. Differentially expressed genes and pathways were investigated and validated using tissue specimens from the xenograft model, 23 patients with matched primary/recurrent tumors, and a cohort including 190 glioblastoma patients. Functional investigations were performed in vitro with multiple patient-derived cell cultures.

Tumor resection induced microglia/macrophage infiltration, angiogenesis as well as proliferation and upregulation of several stem cell related genes in recurrent tumor cells. Expression changes of selected genes SOX2, POU3F2, OLIG2 and NOTCH1 were validated at the protein level in xenografts and early recurrent patient tumors. Single cell transcriptomics revealed presence of distinct phenotypic cell clusters in recurrent tumors which deviated from clusters found in primary tumors. Recurrent tumors expressed elevated levels of pleiotrophin (PTN), secreted by both tumor cells and tumor-associated microglia/macrophages. Mechanistically, PTN could induce tumor cell proliferation, self-renewal and the stem cell program. In glioblastoma patients, high PTN expression was associated with poor overall survival, and identified as an independent prognostic factor.

Surgical tumor resection is an iatrogenic driver of PTN-mediated self-renewal in glioblastoma tumor cells that promotes therapeutic resistance and tumor recurrence [1].

1)
Knudsen AM, Halle B, Cédile O, Burton M, Baun C, Thisgaard H, Anand A, Hubert C, Thomassen M, Michaelsen SR, Olsen BB, Dahlrot RH, Bjerkvig R, Lathia JD, Kristensen BW. Surgical resection of glioblastomas induces pleiotrophin-mediated self-renewal of glioblastoma stem cells in recurrent tumors. Neuro Oncol. 2021 Dec 29:noab302. doi: 10.1093/neuonc/noab302. Epub ahead of print. PMID: 34964899.